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<b>(21) International Application Number:</b> PCT/US96/08119 <b>(22) International Filing Date:</b> 29 May 1996 (29.05.96)  <b>(30) Priority Data:</b> 08/488,675      7 June 1995 (07.06.95)      US  <b>(71) Applicant:</b> INSITE VISION INCORPORATED [US/US]; 965 Atlantic Avenue, Alameda, CA 94501 (US).  <b>(72) Inventors:</b> BOWMAN, Lyle, M.; 5135 Mount Tam Circle, Pleasanton, CA 94566 (US). PATEL, Rajesh, A.; 2151 Vista del Mar, San Mateo, CA 94404 (US). OTTOBONI, Thomas, B.; 1211 North Road, Belmont, CA 94002 (US).  <b>(74) Agent:</b> FREED, Joel, M.; Howrey & Simon, 1299 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUSTAINED RELEASE OPHTHALMIC EMULSIONS  <b>(57) Abstract</b>  Ophthalmic methods and compositions are disclosed where particles of the dispersed phase of emulsions are themselves dispersed and stably maintained in physical separation by lightly crosslinked, water swellable polymers present in an aqueous polymeric system formulated for administration to the eye in drop or ribbon form. Medicament is dissolved in that dispersed phase is delivered over a sustained release period.		

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## SUSTAINED RELEASE OPHTHALMIC EMULSIONS

### Field Of The Invention

This invention relates to topical ophthalmic preparations and methods. More particularly, this invention relates to topical ophthalmic preparations and methods involving medicaments that are not very soluble in aqueous media.

### Background Of The Invention

Oily drugs such as protoglandins (PGs) have been recognized as useful for the reduction of intraocular pressure if topically applied. Their preferred administration in aqueous solutions has also been recognized. See U.S. Patent No. 4,952,851. Isotonization agents such as sodium chloride and thickening agents such as carboxyvinyl polymer, together with buffering agents, stabilizers, etc. have also been proposed for their formulation in ophthalmic compositions. Oil diluents for nonaqueous solutions and suspensions have also been proposed. See U.S. Patent No. 5,405,846.

However, oily drugs present solubility problems in aqueous media, and they are not readily dispersed in such media. Surfactants can be employed to form emulsions in which the oily drugs are dissolved or suspended. See U.S. Patent No. 4,347,238. However, stability of the emulsion can then become a problem. Over time, oily particles forming the disperse phase of the emulsion can agglomerate or coalesce and separate from the aqueous continuous phase. The presence of salts and/or soluble polymers used to increase viscosity can exacerbate the problem by competing for water, thereby increasing the tendency of the oily disperse phase to separate from the aqueous continuous phase. Indeed, avoidance of large quantities (i.e., greater than 0.3%) of the salt of a lightly cross-linked polyacrylic acid has been recommended because of a tendency to gel the water phase, making the emulsion immobile. See U.S. Patent No. 4,347,238 at col. 3, lines 7-10.

Furthermore, the irritating effect of ionic surfactants has been said to be a limiting factor on commercialization of ophthalmic compositions in the form of oil-in-water emulsions. See International Publication WO 94/05298 (PCT/US93/00044).

5        One approach proposed for overcoming some of the foregoing difficulties is the conversion of classical emulsions to submicron emulsions comprising an oil, a phospholipid, a non-ionic surfactant and an aqueous component. Unexplained soothing effects were attributed to the colloidal particles, regardless of whether hydrophobic drugs contained in the particles  
10       or hydrophilic drugs soluble in the aqueous component are employed. See WO 94/05298 at application page 8.

      Despite the promise of such advantages, potential problems associated with settling of particles and/or their agglomeration might still be encountered. Moreover, such problems could still be exacerbated in the  
15       presence of salts and/or soluble polymers used to enhance viscosity.

      It would, therefore, be desirable to overcome or ameliorate drawbacks of the sort previously noted, especially when dealing with oily medicaments.

      It would also be desirable to enhance the bioavailability of solid medicaments of the type which are only sparingly soluble in water. Such  
20       drugs have been satisfactorily dispersed in aqueous polymeric systems of the sustained release type, such as those based on the disclosure of commonly assigned U.S. Patent No. 5,192,535. However, the bioavailability of the drugs during the sustained release period is inhibited by their weak solubility.

### Objects And Summary

25       It is a general object of the present invention to provide novel methods and compositions which provide for sustained release aqueous polymeric systems containing emulsions to be advantageously employed in topical ophthalmic applications.

      It is another object of the present invention to provide novel methods  
30       and compositions wherein the ability to effectively administer oily medicaments is enhanced.

It is an additional object of the present invention to provide novel methods and compositions wherein the tendency of oily medicaments to separate and/or agglomerate in aqueous media is inhibited.

It is a further object of the present invention to provide novel methods  
5 and compositions that enhance the ability to effectively use solid medicaments of the type that are only weakly water soluble.

It is yet a further object of the present invention to enhance the bioavailability, during a sustained release period, of such solid medicaments.

The foregoing and other objects and advantages are intended to be  
10 realized through preferred forms of the invention wherein particles of the dispersed phase of an emulsion of water and oil and/or lipids, are themselves dispersed and maintain in stable physical separation by a lightly crosslinked, water swellable polymer present in the aqueous polymeric system in an amount in excess of .3%, more preferably in excess of .5%, by weight of the  
15 composition. Preferably, the polymer is polyacrylic acid crosslinked with divinyl glycol.

In the most preferred forms of the invention, the disperse phase of the emulsion contains dissolved medicament selected from oily medicaments (e.g., prostaglandins) and solid medicaments sparingly soluble in water (e.g.,  
20 21-aminosteroids).

The pH and osmolality of the composition is adjusted for compatibility with the eye, and a suitable viscosity is established for administration to the eye in drop or ribbon form.

#### Detailed Description

25 In accordance with the present invention, water, an oil and/or lipid, a lightly cross-linked, water swellable polymer, and a medicament are combined in an aqueous system. Particles of the disperse phase of the emulsion are themselves dispersed in that aqueous polymeric system so as to enhance maintenance of the physical separation of such particles.

30 Rather than using large quantities of the polymer, the present invention relies on including an amount of the polymer sufficient to stably

maintain that physical separation of the particles of the disperse phase of the emulsion within the aqueous polymeric system. At least about .5% by weight of the total product is preferred. Generally, the range of polymer will be between about .5% to about 6.5%, usually about .5% to about 2.0%.

5       The emulsion may be based on oils and/or lipids, with use of lipids being preferred. However, any suitable oils or lipids will suffice. Examples of suitable oils include vegetable oils, mineral oils, medium chain triglyceride oils (which may be a component of vegetable oil), oily fatty acids, and mixtures of any of them. For additional identification of suitable oils, see the  
10       disclosures of oils in U.S. Patent No. 4,347,238 at Col. 3, U.S. Patent No. 5,405,846 at Col. 6, and International Publication WO 94/05298 at application pages 9-10, which are all hereby incorporated by reference. Preferred lipids are phospholipid compounds or mixtures of phospholipids such as lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures thereof. See the  
15       disclosure of examples of such compounds or mixtures at application page 10 of International Publication WO 94/05298 which is hereby incorporated by reference. Most preferred is a phospholipid emulsion commercially available under the brand name INTRALIPID.

20	Soybean Oil	10.0g
	Phospholipids	
	(from powdered egg yolk)	1.2g
	Glycerin, USP	2.25g
	Water for injection	qs

25       The pH of INTRALIPID normally ranges from about 6.0 to about 8.9 but the pH may readily be adjusted in a conventional manner such as by the addition of sodium hydroxide.

      Since the lipids already contain hydrophilic functionalities, surfactants may not be necessary or even desirable when lipids alone form the disperse  
30       phase of the emulsion. However, surfactants may still be employed; and when oil is a substantial component of the disperse phase of the emulsion, surfactants generally will be employed. Preferred surfactants are non-ionic, and generally a non-ionic oxide condensate of an organic compound which contains one or more hydroxyl groups will be selected. Polysorbate 80 is

most preferred. For additional identification of suitable surfactants, see the disclosure of surfactants in U.S. Patent No. 4,347,238 at column 3 and in the International Publication WO 94/05298 at application pages 10-11 which are hereby incorporated by reference. Generally, the more oil present the more surfactant would be employed. However, the mechanical separation of particles of the disperse phase of the emulsion in the aqueous polymeric system in accordance with the present invention permits use of comparatively less surfactant, thereby reducing irritation potential.

The emulsions employed in carrying out the present invention include both macroemulsions and microemulsions. It is believed that, from the outset of administration and throughout sustained release, macroemulsions whose disperse phase particles are themselves dispersed in the aqueous polymer system will present benefits in being soothing to the eye. However, it is believed that microemulsions will present additional comfort benefits by reason of either the smaller particle size or the previously mentioned, unexplained physiological mechanism mentioned in International Publication WO 94/052989, or both.

The amount of oil and/or lipid which establishes the disperse phase of the emulsion can be varied. Generally, it will range from about 0.1% to about 60% by weight of the entire composition preferably about 1% to about 20% of the entire composition. Surfactants, when employed, will generally amount to less than about 1.0% by weight of the entire composition, preferably in the range of from about .001% to about .2%.

The aqueous phase of the emulsion will preferably be comprised of distilled water and sodium chloride and will preferably be maintained isotonic with the lacrimal fluid. Osmotic pressure may be adjusted to a pressure of from about 10 to about 400 OsM, more preferably from about 100 to about 300 OsM, and pH will be controlled to be in any range acceptable for administration to the eye, generally a range of about 5.0 to about 9.0. Suitable adjuvants and excipients may also be employed. Typical such additives may include sodium edetate (EDTA), mannitol, sodium hydroxide, and preservatives like benzalkonium chloride (BAK).

The lightly crosslinked polymer systems preferred for use in the present invention are the aqueous suspensions of carboxyvinyl polymers described in U.S. Patent No. 5,192,535, whose entire disclosure concerning their preparation, characteristics and properties is incorporated herein by reference. However, any other suitable lightly crosslinked, water soluble polymer may be employed, for example, polyhydroxyethylmethacrylate or polyvinyl pyrrolidone. The amount of water swellable polymer will preferably range from greater than 0.3% to about 6.5% by weight and preferably from about .5% to about 4.5% by weight, and more preferably from about 1.0% to about 2.0% of the total composition. Most preferably, the polymer is polycarbophil, a polyacrylic acid polymer lightly crosslinked with divinyl glycol.

The viscosity of the aqueous suspension of the polymer will be desirably adjusted in a conventional manner to be in a range suitable for convenient administration to the eye in drop or ribbon form. Generally, that viscosity will be in the range of about 1,000 to about 100,000 centipoises.

It is envisioned that certain benefits of the present invention can be realized independently of the medicament and its solubility. Overall, drug content will vary, usually from about .001% to about 10%, by weight of the entire composition.

In its most preferred form, however, the benefits of the present invention will be realized through implementation with oily drugs that are dissolved in the oil and/or lipid. Prostaglandins and derivatives thereof are especially preferred medicaments envisioned for use, alone or in combination therapy, in that implementation of the present invention. As used herein, the term oily medicament means a medicament that is hydrophobic and that is liquid at physiological pH, temperature and osmolality. The freebase form of pilocarpine also constitutes an oily drug. Other examples will be recognized by those skilled in the art.

Prostaglandins (PGs) were initially isolated from sheep seminal vesicles and human seminal fluid but may be found in most mammalian



tissues. They are a group of eicosanoids which contain cyclical fatty acids, including chain moities, and are known to possess diverse biological activities. These activities include stimulation of smooth muscle, dilation of small arteries, bronchial dilation, and lowering of blood pressure, among  
5 others.

The primary PGs are classified based on the structural feature of a 5-membered cyclical moiety into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs, and PGJs. They are further classified based on the presence or absence of unsaturation and oxidation in the chain moiety using  
10 subscripts 1, 2 and 3 to designate the location of unsaturation and oxidation. They are further subclassified according to the configuration of a hydroxy group into alpha and beta configurations. The chemical structure and classification of these compounds are known and are described, for instance, in U.S. Patent No. 5, 405, 846, the disclosure of which is incorporated herein  
15 by reference. Other patents describing prostaglandins and their use, either alone or in combination with other medicaments, are disclosed in the above-referenced patent and in U.S. Patent No. 4, 599, 353; U.S. Patent No. 4,952, 581; and U.S. Patent No. 4,883,819; the disclosures of which are incorporated herein by reference.

20 As the foregoing patents indicate, prostaglandins and their derivatives and conjugates are particularly useful for the reduction of intraocular pressure when applied to the surface of the eye. Moreover, prostaglandins may be combined with other drugs, such as adrenergic blocking agents, to relieve intraocular pressure. It is contemplated that any of the prostaglandins  
25 and their derivatives and conjugates may be used alone or in combination with other drugs in accordance with the present invention. Formulations of the present inventions incorporating prostaglandins, either alone or in

combination with other drugs, are particularly useful for the reduction of intraocular pressure caused by chronic glaucoma.

5 The amount of any oily medicament employed will vary depending on solubility in the disperse phase of the emulsion. Complete solubility is preferred. In addition, use of an amount of oily medicament that would establish a saturated solution in the given quantity of oil and/or lipid could be desirable. However, consideration of activity and irritation propensity will also govern the medicament content. For example, prostaglandins are  
10 irritating at high concentrations in the eye and have high activity at low concentrations, so an amount of .005% or less, down to about .001% is preferred.

Especially significant benefits of the present invention are also envisioned where the medicament is a solid drug that is only weakly soluble  
15 in water, but quite soluble in the oil and/or lipid. Such drugs, for example, fluoromethalone, have been satisfactorily suspended in aqueous polymeric suspensions of polycarbophil for sustained delivery. However, when dissolved in the oil and/or lipid in accordance with the present invention, their bioavailability to the targeted issue may be enhanced. Since dissolution  
20 from a solid is not then required, the transfer rate into an aqueous phase may be enhanced so a higher permeation may be achieved, thereby by presenting a higher concentration of dissolved drug to the targeted tissue during the sustained release. Other examples of solid drugs which are weakly soluble in water, and whose bioavailability can be similarly enhanced by dissolution in  
25 the oil and/or lipid, will be recognized and appreciated by those skilled in the art.

The following Table I provides examples of compositions that can be used to administer oily medicaments alone or in combination therapy in accordance with the present invention.

**TABLE I**  
**OILY COMPOUNDS/COMBINATIONS**  
 Composition  
 Weight %

5

<u>Component</u>	<u>Example 1</u>	<u>Example 2</u>	<u>Example 3</u>	<u>Example 4</u>	<u>Example 5</u>
PGF <sub>2α</sub> -1-Isopropyl Ester	0.005	-	-	0.005	0.005
Pilocarpine	-	2.0	-	-	-
Scopolamine	-	-	0.25	-	-
Levobunolol HCl	-	-	-	0.1	-
Timolol Maleate	-	-	-	-	0.25
EDTA	0.1	0.1	0.1	0.1	0.1
Sodium Chloride	0.2	-	0.2	0.2	0.2
Mannitol	-	2.0	-	-	-
Polycarbophil	1.2	1.15	1.15	1.2	1.2
Oil/Lipids	1	5	10	5	5
BAK	0.005	0.005	0.005	0.008	0.008
Sodium Hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water	q.s. 100	q.s. 100	q.s. 100	q.s. 100	q.s. 100
pH	6.0	5.4	5.5	6.0	6.0

TABLE I - CONTINUED

<u>Component</u>	<u>Example 6</u>	<u>Example 7</u>	<u>Example 8</u>	<u>Example 9</u>
21-Aminosteroid (U74006F)	0.25	-	-	-
Batismastat - *	-	0.3	-	-
Fluorometholone	-	-	0.1	-
Lexipafant - **	-	-	-	0.3
EDTA	0.1	0.1	0.1	0.1
Sodium Chloride	0.2	0.2	0.2	0.2
Polycarbophil	1.0	1.15	1.2	1.3
Oil/Lipids	20	10	10	20
BAK	0.005	0.005	0.005	0.005
Polysorbate 80	0.2	-	-	-
Sodium Hydroxide	q.s	q.s	q.s	q.s
Purified Water	q.s 100	q.s 100	q.s 100	q.s 100
pH	6.0	6.0	5.6	6.0

\* The chemical name is: [4-(N-hydroxyamino)-2R-isobutyl-3S-(thienylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide

- 5 \*\* The chemical name is: (S)-4-methyl-2-[methyl-[4-(2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzenesulfonyl]-amino]-pentanoic acid ethyl ester

The Examples 1-9 listed in Table I can be prepared on a 100gm scale in the following manner:

1. An oil phase containing triglyceride, oily medicament or water insoluble drug, and lipid is heated to about 50°C.
- 5 2. An aqueous phase, containing water, isotonic agent, EDTA, and water soluble non-ionic surfactant, is heated to about 50°C.
3. The two phases are combined together, mixing well with a magnetic stirrer to produce a coarse emulsion. The emulsion is further heated to about 80°C.
- 10 4. The emulsion is homogenized by a homogenizer at 10,000 rpm for 3 minutes and then rapidly cooled to below 40°C in an ice bath.
5. After cooling, the emulsion is sonicated by a probe ultrasonic processor for 5-10 minutes until a translucent microemulsion is obtained. The pH adjustment to the target pH is made after the sonication step.
- 15 6. A polymer system is prepared separately by hydrating the polymer in water and then adding EDTA, isotonic agent, and water soluble drug.
7. The pH of the polymer system is adjusted to target pH of the formulation with NaOH.
8. The microemulsion is added to the polymer system and these components are mixed.
- 20

The foregoing Examples are illustrative and are not to be considered limiting of the present invention. Departure from specifics set forth either in those examples or elsewhere herein can be made without departing from the spirit and scope of the invention as defined in the appended claims.

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**WHAT IS CLAIMED IS:**

1. A topical ophthalmic composition comprising an aqueous polymeric system wherein particles of the disperse phase of an oil, lipid, or oil and lipid emulsion, are themselves dispersed and maintained in stable,  
5 physical separation by a lightly crosslinked, water swellable polymer present in an amount in excess of .3% by weight of the composition.
2. A topical ophthalmic composition according to Claim 1 wherein said polymer is present in an amount in the range of about .5% to about 6.5% by weight of the composition.
- 10 3. A topical ophthalmic composition according to Claim 2, wherein said polymer is present in an amount in the range of about .5% to about 2.0% by weight of the composition.
4. A topical ophthalmic composition according to Claim 1, wherein said polymer is present in at least about .5% by weight of the  
15 composition.
5. A topical ophthalmic composition according to Claim 4, wherein said polymer is a carboxyvinyl polymer.
6. A topical ophthalmic composition according to Claim 5, wherein said polymer is polycarbophil.
- 20 7. A topical ophthalmic composition according to Claim 6, further comprising an oily medicament dissolved in said dispersed phase of the emulsion.
8. A topical ophthalmic composition according to Claim 6, wherein a prostaglandin is dissolved in said dispersed phase of the emulsion.
- 25 9. A topical ophthalmic composition according to Claim 8, wherein said emulsion is a microemulsion of water and phospholipid compounds or mixtures of phospholipids, essentially free of surfactants.

10. A topical ophthalmic composition according to Claim 6 further comprising a solid medicament sparingly in water and contained in solution in the disperse phase of the emulsion.

11. A topical ophthalmic composition according to Claim 1, further  
5 comprising an oily medicament dissolved in said dispersed phase of the emulsion.

12. A topical ophthalmic composition according to Claim 1, wherein a prostaglandin is dissolved in said dispersed phase of the emulsion.

13. A topical ophthalmic composition comprising an emulsion of  
10 oil, lipid or oil and lipid whose dispersed phase contains dissolved medicament and is dispersed in an aqueous suspension of a lightly crosslinked water swellable polymer present in excess of about .5% by weight of the composition, and wherein the pH is in the range of about 5.0 to about 9.0, the osmolality is in the range of about 10 to about 400 OsM, and the  
15 viscosity is suitable for administration to the eye in drop or ribbon form for sustained release of the medicament.

14. A topical ophthalmic composition according to Claim 13, wherein said polymer is polycarbophil.

15. A topical ophthalmic composition according to Claim 14 further  
20 comprising an oily medicament dissolved in said dispersed phase of the emulsion.

16. A topical ophthalmic composition according to Claim 14 further comprising a solid medicament sparingly soluble in water and contained in solution in the dispersed phase of the emulsion.

17. A topical ophthalmic composition according to Claim 13 further  
25 comprising an oily medicament dissolved in said dispersed phase of the emulsion.

18. A topical ophthalmic composition according to Claim 13 further comprising a solid medicament sparingly soluble in water and contained in solution in the dispersed phase of the emulsion.

19. A topical ophthalmic composition according to claim 14  
5 wherein said medicament comprises a prostaglandin.

20. A topical ophthalmic composition comprising:  
an aqueous suspension of a lightly crosslinked water swellable  
polymer present in the range of from about .5% to about 6.5% of the  
composition, and  
10 an aqueous microemulsion of water and phospholipid compounds or  
mixtures of phospholipids, essentially free of surfactants, and whose disperse  
phase contains dissolved medicament, selected from oily medicaments and  
solid medicaments weakly soluble in water;  
particles of the dispersed phase of the microemulsion being dispersed  
15 and maintained in stable, physical separation by the polymer, and the  
viscosity of the composition being suitable for administration to the eye in  
drop or ribbon form for sustained release of the medicament.

21. A topical ophthalmic composition according to Claim 20,  
wherein said dissolved medicament comprises a prostaglandin, and said  
20 polymer is polycarbophil.

22. A topical ophthalmic composition according to Claim 20,  
wherein said dissolved medicament fluoromethalone or pilocarpine, and said  
polymer is polycarbophil.

23. A topical ophthalmic composition as recited in claim 21,  
25 wherein said phospholipid compounds or mixtures of phospholipids  
comprise about 0.1% to about 60% of said composition.

24. A topical ophthalmic composition as recited in claim 21,  
wherein said phospholipid compounds or mixtures of phospholipids  
comprise about 1% to about 20% of said composition.



25. A method of administering an oily medicament or a medicament sparingly soluble in water, comprising:

dissolving at least some of the medicament in the dispersed phase of an emulsion,

5       dispersing the emulsion in an aqueous suspension of a lightly crosslinked, water swellable polymer, and

administering the emulsion to the eye, as so dispersed, in drop or ribbon form for delivery of the medicament over a sustained release period.

26. A method of preparing a topical ophthalmic composition for

10       administration to the eye comprising:

dissolving at least some medicament in the dispersed phase of an emulsion,       dispersing the dispersed phase of the emulsion in an aqueous suspension of a lightly crosslinked, water swellable polymer,

adjusting the ph and osmolality for compatibility with the eye, and

15       establishing a viscosity of the system for administration to the eye in drop or ribbon form.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/08119

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 05163 (PHARMOS CORPORATION) 23 February 1995	1-26
Y	see claims 1-3,10,22,23 see page 4, line 22 - line 29 see page 6, line 1 - line 27 see page 7, line 3 - line 8 see page 8, line 6 - page 10, line 22 see page 12, line 23 - page 13, line 9 see page 18; example 6.1 ---	22
X	EP,A,0 063 870 (SUMITOMO CHEMICAL COMPANY) 3 November 1982	1-5,11, 13,20, 25,26 22
Y	see claims 1,2,4 see page 6; example 2 -----	

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

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# INTERNATIONAL SEARCH REPORT

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Int. Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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